

Attorney Docket No.: 5386.224-US
Application Serial No.: 10/083,058
Filed: February 25, 2002
Inventors: Havelund et al.

Amendments To The Claims

The listing of claims will replace all prior versions, and listings, of the claims in the application.

Listing Of Claims:

Claims 1-69 (Cancelled)

Claim 70 New) A method for producing a pharmaceutical preparation of a derivative of human insulin or a human insulin analog, said method comprising determining that the derivative contained in said preparation forms a water-soluble aggregate which has a size larger than aldolase.

Claim 71 (New) The method of claim 70, wherein the size of said aggregate is determined in a gel filtration system.

Claim 72 (New) The method of claim 70, wherein it is further determined that said aggregate has a size larger than ferritin.

Claim 73 (New) The method of claim 70, wherein it is further determined that the water-soluble aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.32 as determined by gel filtration using a Sephacryl[®] S-300 HR gel.

Claim 74 (New) The method of claim 70, wherein it is further determined that the water-soluble aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.20 as determined by gel filtration using a Sephacryl[®] S-300 HR gel.

Claim 75 (New) The method of claim 70, wherein it is further determined that the water-soluble aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.50 as determined by gel filtration using a Superose[®] 6HR gel.

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Claim 76 (New) The method of claim 70, wherein it is further determined that the water-soluble aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.40 as determined by gel filtration using a Superose[®] 6HR gel.

Claim 77 (New) The method of claim 70, wherein the derivative in said aggregate has a lipophilic group of 12 to 36 carbon atoms attached, optionally via a spacer, to a lysine residue of said insulin or insulin analog.

Claim 78 (New) The method of claim 77, wherein the derivative is a derivative of human insulin.

Claim 79 (New) The method of claim 78, wherein the lipophilic group attached, optionally via a spacer, to a lysine residue of said insulin is 5- α lithocholic acid or 5- β lithocholic acid.

Claim 80 (New) The method of claim 79, wherein the lipophilic substituent 5- α lithocholic acid or 5- β lithocholic acid is linked to the lysine residue through an amino acid linker.

Claim 81 (New) The method of claim 80, wherein the amino acid linker is selected from the group consisting of γ -glutamyl, β -aspartyl and α -aspartyl.

Claim 82 (New) The method of claim 77, wherein the derivative is a derivative of a human insulin analog.

Claim 83 (New) The method of claim 82, wherein the total number of amino acid differences between the amino acid sequence of the insulin analog and the amino acid sequence of insulin is four and where the amino acid differences are at amino acid

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residues of insulin selected from the group consisting of A21, B1-B3, B13, and B24-B30.

Claim 84 (New) The method of claim 83, wherein the amino acid differences between the amino acid sequence of the insulin analog and the amino acid sequence of insulin are at amino acid residues of insulin selected from the group consisting of A21, B1, B28, B29 and B30.

Claim 85 (New) The method of claim 83, wherein residues B24-B30 of the insulin analog have the sequence Phe-X-X-X-X-X-X where X is any codable amino acid or a deletion.

Claim 86 (New) The method of claim 85, wherein the X at residue B30 is deleted.

Claim 87 (New) The method of claim 86, wherein the X at residue B29 is Lys and is the lysine residue to which the lipophilic group is attached.

Claim 88 (New) The method of claim 85, wherein the lipophilic group attached, optionally via a spacer, to a lysine residue of said insulin is 5- α lithocholic acid or 5- β lithocholic acid.

Claim 89 (New) The method of claim 88, wherein the lipophilic substituent 5- α lithocholic acid or 5- β lithocholic acid is linked to the lysine residue through an amino acid linker.

Claim 90 (New) The method of claim 89, wherein the amino acid linker is selected from the group consisting of γ -glutamyl, β -aspartyl and α -aspartyl.

Claim 91 (New) The method according to claim 83, wherein it is further determined that the water soluble aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.32 as determined by gel filtration using a Sephacryl[®] S-300 HR gel.

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Claim 92 (New) The method according to claim 83, wherein it is further determined that the water soluble aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.20 as determined by gel filtration using a Sephacryl® S-300 HR gel.

Claim 93 (New) The method according to claim 83, wherein it is further determined that the water soluble aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.50 as determined by gel filtration using a Superose® 6HR gel.

Claim 94 (New) The method according to claim 83, wherein it is further determined that the water soluble aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.40 as determined by gel filtration using a Superose® 6HR gel.